

APPENDIX TO SUBSTITUTE SPECIFICATION FILED JANUARY 25, 2002
VERSION WITH MARKINGS TO SHOW CHANGES MADE

Amendments to the Specification

Please replace paragraph 003 with the following amended paragraph:

--[003] These diseases generally occur in areas of the body which contain a high proportion of collagen, a particular form of connective tissue. An examination of patients with these diseases of connective tissue has revealed an excessive breakdown of the various components of connective tissues, including collagen proteoglycans and elastin. Therefore, it has been deduced that an excessive concentration of a particular metalloproteinase, for example collagenase, [proteoglyconuse] proteoglyconase, gelatinase, and certain elastases, may cause or exacerbate the connective tissue destruction associated with the aforementioned diseases.--

Please replace paragraph 028 with the following amended paragraph:

--[028] As noted above, the present invention relates in part to portable DNA sequences capable of directing intracellular production of metalloproteinase inhibitors in a variety of host microorganisms. "Portable DNA sequence" in this context is intended to refer either to a synthetically-produced nucleotide sequence or to a restriction fragment of a naturally occurring DNA sequence. For purposes of this specification, "metalloproteinase inhibitor" is intended to mean the primary structure of the protein as defined by the codons present in the deoxyribonucleic acid sequence which directs intracellular production of the amino acid sequence, and which may or may not include

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post-translational modifications. It is contemplated that such post-translational modifications include, for example, glycosylation. It is further intended that the term "metalloproteinase inhibitor" refer to either the form of the protein as would be excreted from a microorganism or the methionyl-metallo[-]proteinase inhibitor as it may be present in microorganisms from which it was not excreted.--

Please replace paragraph 032 with the following amended paragraph:

--[032] In this second preferred sequence, an open reading frame exists from nucleotides 1 through 432. The first methionine of this reading frame is encoded by nucleotides [by] 49 through 51 and is the site of translation initiation. It should be noted that the amino acid sequence prescribed nucleotides by 49 through 114 is not found in the mature metalloproteinase. It is believed that this sequence is the leader peptide of the human protein.--

Please replace paragraph 085 with the following amended paragraph:

--[085] In a preferred embodiment, the signal peptide of the *E. coli* OmpA protein is used as a leader sequence and is located in a position contiguous with the portable DNA sequence coding for the [metalloproteinese] metalloproteinase inhibitor structure.

Please replace paragraph 102 with the following amended paragraph:

--[102] EXAMPLE 2-EXPRESSION OF [COLLAGENESE] COLLAGENASE INHIBITOR IN *E. COLI*--

Please replace paragraph 140 with the following amended paragraph:

--[140] It will be apparent to those skilled in the art that various modifications and variations can be made in the processes and products of the present invention. Thus, it is intended that the present invention cover the modifications and variations of this

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invention provided they come within the scope of the appended claims and their
[equivalence] equivalents.--

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